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FACSIMILE INFORMATION SHEET

RESPONSE UNDER 37 C.F.R §1.116
EXPEDITED PROCEDURE
GROUP ART UNIT 1617

Name of Individual: MAIL STOP AF
Commissioner for Patents

Company: United States Patent and Trademark Office
City and State: Alexandria, VA

Facsimile Number: 703-872-9306

From: Ann M. Cannoni, Esquire

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Date Transmitted: July 8, 2005

CV01379K US
Client No.: 4686 File No.: 045566

Message:

Application No. 10/057,646
Inventors: Harry R. Davis
Filed: January 25, 2002
Title: COMBINATIONS OF NICOTINIC ACID AND DERIVATIVES THEREOF AND STEROL ABSORPTION INHIBITOR(S) FOR VASCULAR INDICATIONS

Transmittal Form (1p)
Request for Reconsderation (8pp)

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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/057,646
Filing Date	January 25, 2002
First Named Inventor	Harry R. Davis
Art Unit	1617
Examiner Name	Shengjun Wang
Total Number of Pages in This Submission: 9	Attorney Docket Number: CV01379US/4686-045566

ENCLOSURES (Check all that apply)

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☒ Amendment/Reply
  - ☒ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Documents
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition to Reinstate
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s)_____
- ☐ After Allowance communication To Technology Center (TC)
- ☐ Appeal Communication to Board Of Appeals and Interferences
- ☐ Appeal Communication to TC (Appeal Notice, Brief, Reply Brief)
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please identify below)

Remarks

Firm Or Individual name	Ann M. Cannoni The Webb Law Firm
Signature	
Date	July 8, 2005

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Signature	Chris Craig	Date	7/8/2005

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Application No. 10/057,646
Paper Dated: July 8, 2005
Reply to Office Action of May 10, 2005

MAIL STOP AF

RESPONSE UNDER 37 C.F.R. § 1.116

EXPEDITED PROCEDURE EXAMINER GROUP ART UNIT 1617

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Patent Application of Harry R. Davis et al.	: PATENT APPLICATION
Serial No.: 10/057,646	: Group Art Unit: 1617
Filed: January 25, 2002	: Examiner: Shengjun Wang
For: Combinations of Nicotinic Acid and Derivatives Thereof and Sterol Absorption Inhibitor(s) and Treatments for Vascular Indications	: Atty. Docket No.: CV01379K

MAIL STOP AF
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

REQUEST FOR RECONSIDERATION

This Amendment is being submitted in response to the final Office Action mailed on May 10, 2005.

I hereby certify that this correspondence is being transmitted via facsimile addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, facsimile number 703-872-9306 on July 8, 2005

Chris Craig
(Name of Person Faxing Paper)

Chris Craig
Signature

7/8/2005
Date

Claims 1-4, 7-10, 28-30 and 32 are pending in the application. Claims 11-27, 36-39, 41, 44-46, 51, 54, 56, 59, 61, 64, 66, 69, 72, 75, 78 and 81 have been withdrawn from consideration by the Examiner as being non-elected. Claims 5, 31 and 33-81 were previously canceled without prejudice to filing one or more divisional applications directed to the subject matter thereof. Claim 6 was canceled without prejudice to filing one or more divisional applications directed to the subject matter thereof.

At pages 2-6 of the Office Action, claims 1-4, 7-10, 28-30 and 32 have been rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,846,966 ("Rosenblum et al.") in view of U.S Patent No. 5,698,527 ("Kim") and WO 2000/38725 ("Keller et al.").

In the rejection, it is asserted that Rosenblum et al. teach the claimed cholesterol absorption inhibitors, their application in lowering cholesterol and combination with other cholesterol lowering agents such as simvastatin. Also, it is alleged that Rosenblum et al. teach a daily dosage of such compounds when used in combination with another drug of about 1 mg to 1000 mg given 1 or 2 times a day. It is expressly acknowledged that Rosenblum et al. do not teach a combination of cholesterol absorption inhibitor and nicotinic acid.

In the rejection, it is alleged that Kim teaches that niacin is a well-known cholesterol lowering agent and is particularly useful in combination with cholesterol absorption inhibitors. It is further alleged that Keller et al. teach various combinations of cholesterol lowering agents, including ezetimibe and nicotinic acid, for treating hypercholesterolemia-associated disorders.

It is alleged that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising ezetimibe and nicotinic acid, and optionally simvastatin, since the compounds are known for use for the same purpose, citing In re Kerkoven. As to the specific amount, it is argued that they amount is within the disclosed range.

Applicants respectfully traverse this rejection and request that the rejection be reconsidered and withdrawn.

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992).

The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d at 1784; In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

"It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious....'[o]ne cannot use hindsight

reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" In re Fritch, 23 U.S.P.Q.2d at 1784 (quoting In re Fine, 5 U.S.P.Q.2d at 1600).

"The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence." Manual of Patent Examining Procedure, (Rev. 1, Feb. 2003) § 716.01(d) and In re Oetiker, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

As shown in Table 1 of the present application, Compound XII (a substituted azetidinone cholesterol absorption inhibitor) reduced plasma cholesterol levels and the accumulation of hepatic cholesteryl esters in the cholesterol-fed hamsters. Niacin reduced plasma triglyceride levels, but did not significantly reduce the cholesterol levels. The combination of Compound XII and niacin resulted in reductions in plasma and hepatic cholesterol levels, as well as plasma triglycerides (Table 1). These results indicate that the combination of the cholesterol absorption inhibitor of Compound XII and niacin can have additive effects on treating hyperlipidemia in male Golden Syrian hamsters, by reducing both cholesterol and triglyceride levels. As is well know to those skilled in the art, the efficacy of combinations of drug compounds can be unpredictable.

Rosenblum et al. do not suggest or disclose the combination of ezetimibe and nicotinic acid. Rosenblum et al. do not suggest or disclose the desirability of a 10 milligram dosage of ezetimibe.

Kim discloses steroidal glycoside cholesterol absorption inhibitors that can be administered in combination with niacin, but does not suggest or disclose combining ezetimibe with niacin or the desirability of the claimed amount of 10 milligrams of ezetimibe. Ezetimibe is not a steroidal glycoside. The steroidal glycosides disclosed by Kim are structurally very dissimilar to the presently claimed substituted azetidinone compound ezetimibe. Given their large molecular size, it is unlikely that Kim's steroidal glycosides are absorbed through the intestine. In contrast, multiple peaks in plasma concentration-time profiles suggest that the glucuronide conjugate of ezetimibe undergoes enterohepatic recycling before elimination. See ZETIA™ (ezetimibe) Tablets Package Insert at column 2 (Merck/Schering-Plough Pharmaceuticals) (October 2002), included in the Information Disclosure Statement of August 30, 2004. This enterohepatic recycling can enhance efficacy. It would not be obvious to one of ordinary skill in the art to substitute ezetimibe disclosed by Rosenblum et al. for the steroidal glycosides disclosed by Kim, since they are likely to be dissimilar in site of action.

Kim's steroidal glycoside compounds have not been commercialized by Merck & Co., Inc. (the assignee of the Kim patent). Rather, Merck is the joint venture partner of Schering-Plough (assignee of the present application) in marketing the cholesterol absorption inhibitor ZETIA™ ezetimibe formulation. ZETIA was launched in late 2002 and global sales of ZETIA in the 2003 fourth quarter totaled $165 million, with U.S. sales of $144 million. Press Release: Schering-Plough Reports Financial Results for 2003 Fourth Quarter,

Full Year (Monday January 26, 6:33 am ET). Thus it can be inferred that Kim's steroidal glycoside compounds were not commercially viable as treatments.

"[S]econdary considerations such as ... commercial success, long-felt need, failure of others ... are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence." M.P.E.P. § 2141 (Rev'd May 2004). Applicants respectfully request that the above information regarding commercial success, long-felt need, and failure of others be considered by the Examiner.

No data is presented in the Kim reference to support efficacy of a combination of steroidal glycoside and niacin. One skilled in the art would not be motivated to combine ezetimibe and nicotinic acid based upon the disclosure of Kim since the steroidal glycoside and ezetimibe molecules are so structurally dissimilar.

Keller et al. disclose combinations of (1) an ileal bile acid transport inhibitor or CETP inhibitor and (2) a cholesterol absorption inhibitor such as ezetimibe, but *not the combination of ezetimibe and nicotinic acid*. Also, Keller does not suggest or disclose the desirability of a 10 mg dosage of ezetimibe.

It is respectfully submitted that the combination of the references cited as rendering the claimed invention obvious is improper because there is no suggestion in the cited references to combine the claimed components of 10 milligrams of ezetimibe and nicotinic acid.

Even if the teachings of the references were combined as set forth in the Office Action, there are not sufficient teachings to motivate one of ordinary skill in the art to combine 10 milligrams of ezetimibe with nicotinic acid.

Neither Rosenblum et al, Kim, nor Keller et al., taken alone or combined as set forth in the Office Action, provides motivation for combining 10 milligrams of ezetimibe and niacin. Also, Applicants respectfully request that the above information regarding commercial success, long-felt need, failure of others be considered by the Examiner. Accordingly, reconsideration and withdrawal of the §103(a) rejection is respectfully requested.

Applicants respectfully request that the Examiner return an initialed PTO-1449 form for the Information Disclosure Statement submitted herewith and each of the Information Disclosure Statements submitted on October 28, 2003, April 12, 2004 and May 13, 2004, indicating that the Examiner has considered each of the references cited therein.

In view of the foregoing remarks, it is respectfully submitted that all of the pending claims in the present application are distinguishable from the cited

prior art. Accordingly, reconsideration and withdrawal of the rejection and an early Notice of Allowance are respectfully requested.

Respectfully submitted,

Date: July 8, 2005

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